REMARKS

Applicant respectfully requests reconsideration. Claims 100-102 and 104-107 were previously pending in this application. Claim 100 is amended to incorporate the limitations of now canceled claim 104. Claim 104 is canceled. New claims 108-118 corresponding to original claims 1- 2, 12, 14, 16, 17, 22, 24, 26, 27, 44, 66, 67, 97, and 98 have been added. Therefore, claims 100-102 and 105-118 are pending for examination with claims 100, 105, 108 and 115-118 being independent claims.

No new matter has been added.

Summary of Telephone Conference with Examiner

Applicant thanks Examiners Archie and Zeman for the Telephone Conference of March 30, 2010. In the Interview, the outstanding obviousness rejection was discussed.

Applicant acknowledges the Interview Summary mailed by the Office on April 9, 2010. The Summary indicates that the Office will review the Samani et al. reference in regards to teaching away from the claimed invention.

New Claims

Claims 108-122 have been added. Claims 108-122 correspond to originally filed claims 1-2, 12, 14, 16, 17, 22, 24, 26, 27, 44, 66, 67, 97, and 98, amended or combined to reflect changes discussed during the interview with the examiner with respect to the pending claims. In particular the stabilized internucleotide linkage is limited to a phosphorothioate linkage and the phosphodiester or phosphodiester-like internucleotide linkage is limited to a phosphodiester linkage. Additionally, claim 1 (now claim 108) was narrowed to limit the YG to CG, as in original claim 12. Specifically, claim 108 finds support in original claims 1, 12, 24, 26 and 27. The claims were part of the elected group I and were pending prior to the Amendment dated March 11, 2009 in which the claims were canceled in order to advance prosecution. Applicant hereby elects to continue prosecution of the full set of claims of Group I.

Rejection Under 35 U.S.C. §103

Claims 100-102 and 104-107 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable in view of Krieg et al. (WO01/22972 A1 April 5, 2001) and Samani et al. (Antisense and Nucleic Acid Drug Development 2001 Vol. 11 pgs. 129-136). According to the Office, Krieg et al. teaches specifically sited phosphodiester or phosphodiester-like internucleotide linkages. Furthermore, according to the Office, Samani et al. teaches that phosphodiesters are rapidly degraded by serum intracellular nucleases. Therefore, according to the Office, one would have been motivated at the time the invention was made to place a phosphodiester between the C and the G to produce an oligonucleotide with a CpG that has a phosphodiester internucleotide linkage and modify the oligonucleotide with stabilized internucleotide linkages such as phosphorothioate as taught by Krieg et al. because Krieg et al. teach a chimeric combination of phosphodiester and phosphorothioate oligonucleotide because a cell may have a problem taking up a plasmid vector in the presence of completely phosphorothioate nucleic acid.

Applicant respectfully traverses. The combination of Krieg et al. (WO01/22972) and Samani et al. does not render obvious the oligonucleotides (and compositions thereof) of the rejected claims at least for the reasons presented below:

1. As discussed in the interview, a combination of Krieg et al. and Samani et al. did not render obvious the rejected claims, because the claimed invention was based on unexpected results that were not obvious to the skilled artisan in view of the cited references at the time of the invention. Namely, the instant application shows that the claimed oligonucleotides (with non-stabilized CpG dinucleotide sequences) have a similar or enhanced *in vivo* activity when compared to an oligonucleotide of the same sequence having only stabilized internucleotide linkages.

At the time of filing of the application the prior art taught that oligonucleotides with stabilized internucleotide linkages have increased immunostimulatory activity as compared to oligonucleotides without stabilized internucleotide linkages. Based on the art at the time of filing of the application, a person of ordinary skill in the art would have expected that replacing a stabilized internucleotide linkage (*e.g.*, a phosphorothioate linkage) with a non-stabilized linkage (*e.g.*, a

phosphodiester linkage) would result in breakage of the oligonucleotide at the phosphodiester linkage, resulting in more rapid degradation of the oligonucleotide. In particular, the skilled artisan would not have placed the phosphodiester linkage within the critical immunostimulatory motif because of the expectation that the oligonucleotide would be susceptible to cleavage within the critical motif and break into shorter oligonucleotides that don't include the critical motif. It would have been expected in the absence of the findings of the invention that placing the phosphodiester linkage between the C and G in the CpG motif would decrease the immunostimulatory activity of an oligonucleotide.

In the interview, Applicants indicated that evidence of the state of the art would be presented in order to establish the baseline for unexpected results. The state of the art at the time of filing is exemplified by the following references (copies of the references are included with this submission).

Krieg et al., (WO01/22972; of record) discloses that non-stabilized oligonucleotides show significantly weaker activity when compared to stabilized oligonucleotides. As stated on page 36, "It is believed that these modified nucleic acids may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization".

Hartmann et al., (J of Immunology 2000, 164: 1617-1624, p1618 left column) state "To have in vivo clinical utility, ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the nonbridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN".

Hartmann et al., (Gene Therapy 1999, 6: 893-903) show that phosphorothioate oligonucleotides are more potent immunostimulants than their phosphodiester counterparts. The authors state "Because of their higher stability, the phosphorothioate-modified ODN were used in a lower concentration (6 microgram/ml) then the unmodified ODN (30 microgram/ml). Furthermore, the unmodified ODN were added repeatedly (0, 4 and 8h)" (page 899, left column). The data presented by the authors in Figs. 9 and 10, shows that phosphorothioate oligonucleotides have

increased immunostimulatory activity, even though the phosphodiester oligonucleotides were administered multiple times at higher concentration.

Parronchi et al., (J of Immunology 1999, 163: 5946-5953) show that phosphorothioate oligonucleotides (PS) have increased immunostimulatory activity compared to their phosphodiester (PE) counterparts "The results of our study first confirm those previously reported in humans, showing that certain synthetic ODNs were able to induce strong proliferative response by purified peripheral blood B cells. Such an immunostimulatory activity was usually associated with nuclease-resistant PS, but not PE, compounds and was abolished by cytosine methylation" (page 5951).

In addition, Samani et al. (of record) teaches that oligonucleotides with stabilized linkages (phosphorothioate linkages) are more effective *in vivo* than oligonucleotides without these linkages. The authors state "They are generally capped at the both ends by PS linkages for protection against 3'- exonuclease degradation (mainly in serum) and 5'-exonuclease degradation (mainly inside the cells)". Furthermore, Samani et al. specifically teaches that stabilization of CpG sites, stabilizes the whole oligonucleotide, "Guanines in CpG sites seem to be significant cleavage sites for K562 endonucleases. Their protection considerably reinforces the stability of the oligonucleotide" (page 135, right column).

Thus, based on the art at the time of filing of the application, a person of ordinary skill in the art would have expected that replacing a stabilized internucleotide linkage (*e.g.,* a phosphorothioate linkage) with a non-stabilized linkage (*e.g.,* a phosphodiester linkage) would decrease the activity of the oligonucleotide.

In contrast, the instant application shows that the claimed oligonucleotides (with non-stabilized CpG dinucleotide sequences) have a similar or enhanced *in vivo* activity when compared to an oligonucleotide of the same sequence having only stabilized internucleotide linkages. See for instance Example 22 on page 101 and accompanying Figure 25. (Applicant notes that in the Amendment filed March 11, 2009, Applicant provides a detailed account of the support in the specification for the unexpected properties of the oligonucleotides of the rejected claims).

Furthermore, the fact that the findings of the invention were surprising to the skilled artisan is shown by the teachings of the peer-reviewed post-filing publication of Krieg et al. (Oligonucleotides, 13: 491-499, December 2003). The authors confirm the state of the art (page

492) "native DNA (PO-DNA) is rapidly degraded by a large number of exonucleases and endonucleases in living cells. Therefore, it may not be surprising that CpG motifs in a nuclease resistant PS backbone have markedly enhanced immune stimulatory effects compared with the same sequences with a PO backbone". The authors then compared a CpG oligonucleotide with a stabilized dinucleotide at CpG (Sp stereoisomer of phosphorothioate) with an oligonucleotide with non-stabilized dinucleotide at CpG (Rp stereoisomer of phosphorothioate). The data presented in Fig.2 show ("Surprisingly", according to the authors) that replacing a stabilized internucleotide linkage at CpG with a non-stabilized internucleotide linkage at CpG, increases the immunostimulatory effect of the oligonucleotide, which is in contrast to the findings in the art at that time.

During the telephone interview the Examiners suggested that Applicant amend the claims to more closely reflect the unexpected results. In particular it was suggested that the claims recite phosphorothioate rather than stabilized and phosphodiester rather than phosphodiester-like. Although Applicant disagrees that such an amendment is necessary, claim 1 has been amended to indicate that the stabilized internucleotide linkage is a phosphorothioate linkage. The claim already recited a phosphodiester internucleotide linkage. The newly added claims also include these limitations. In view of the unexpected results described above, it is believed that the amended claims are allowable over the cited prior art.

2. The combination of Krieg et al. and Samani et al. does not disclose all the elements of the rejected claims. The rejected claims relate to oligonucleotides (and compositions thereof) having the sequence 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T 3' (wherein * refers to the presence of a phosphorothioate internucleotide linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage). In addition, the claimed oligonucleotides and compositions thereof are between 24 and 40 nucleotides in length. Krieg et al. does not disclose an oligonucleotide having the sequence 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_ G*T*T 3' (wherein * refers to the presence of a phosphorothioate internucleotide linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage). Krieg et al. discloses an oligonucleotide with the sequence T*C*G*T*C*G*T*T*T*T*G*A*C*G*T*T*T*T*G*T*C*G

*T*T (SEQ ID NO:343 of WO01/22972). However, this oligonucleotide has a completely stabilized backbone and does not have CpG sequences that have phosphodiester internucleotide linkages. Samani et al. does not provide the missing teaching as Samani et al. does not provide stabilized oligonucleotides wherein the CG sequences have phosphodiester internucleotide linkages. Thus, the combination of Krieg et al. and Samani et al. does not disclose all the elements of the rejected claims.

3. Samani et al. teaches away from the claimed oligonucleotides and compositions thereof. Krieg et al. discloses that stabilized CpG containing oligonucleotides (*e.g.,* comprising phosphorothioate backbones) have enhanced activity when compared to non-stabilized CpG containing oligonucleotides (*e.g.,* comprising phosphodiester backbones). Samani et al. teaches that CpG sites are significant cleavage sites for endonucleases and that their protection considerably reinforces the stability of the oligonucleotide (page 135, second column). Therefore, *arguendo* even if a person of ordinary skill in the art would want to replace a stabilized internucleotide linkage with a phosphodiester linkage, a person of ordinarily skill in the art would want to introduce phosphodiester internucleotide linkages at positions *other than* the CpG dinucleotide sequences. Thus, combining the teachings of Krieg et al. and Samani et al. would result in oligonucleotides wherein the CpG dinucleotide sequence have stabilized internucleotide linkages. In contrast, the oligonucleotides of the rejected claims have CpG dinucleotide sequences with phosphodiester internucleotide linkages.

In addition to the reasons cited above, Applicant believes that the Office has not established a *prima facie* obviousness rejection because the Office has not provided sufficient support for the allegation that the combination of Krieg et al. and Samani et al renders obvious the rejected claims. The Office has misinterpreted the teachings of Krieg et al., and Samani et al., and the Office has provided no rational basis for combining the teachings of Krieg et al. and Samani et al. to establish an obviousness rejection.

The Office states that "Krieg et al. teaches an oligonucleotides comprising the formula N_1-C_G-N_2-C_G-$N_3$3, wherein N_1, N_2 and N_3 are each independently a nucleic acid sequence of 0-20 nucleotides in length and wherein _ indicates an internal phosphodiester internucleotide linkage (see

pages 2-12, pgs. 18-24, pgs. 27-30, and pg. 34), wherein the immunostimulatory nucleic acids molecule is 4-100 nucleotides long (see pg. 8 lines 8-13)". Applicant has reviewed the cited pages of Krieg et al., but did not find such statements. Thus, the Office's inference that "Therefore Krieg et al. teach specifically sited phosphodiester or phosphodiester-like internucleotide linkages" does not follow from the cited teachings of the art. During the interview the Examiners indicated that this issue would be reviewed and that the proper citation would be provided to Applicant. Applicant has not yet received that information.

Furthermore, the Office reasons that stabilized oligonucleotides may be modified at the CpG dinucleotide "because a cell may have a problem taking up a plasmid vector in the presence of completely phosphorothioated nucleic acids". Even if, *arguendo*, a cell may have a problem taking up a plasmid vector in the presence of completely phosphorothioated nucleic acid, it is unclear why such a statement has any relation to the oligonucleotides and compositions of the rejected claims. The rejected claims do not relate to methods of taking up plasmids into cells. The claims relate to oligonucleotides and compositions thereof.

Thus, the Office has not met the burden of establishing a *prima facie* obviousness rejection.

Finally, Applicant believes that the Office has not fully considered the arguments presented by Applicant in the previous response. As stated in the MPEP (§2145) Office personnel should consider all rebuttal arguments and evidence presented by applicants. See, e.g., *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687). While the Office Action reproduces the arguments presented previously by Applicant (See page 3-4), the Office Action does not discuss the substance of the arguments presented by Applicant.

Thus, for the reasons presented above, the combination of Krieg et al. (WO01/22972) and Samani et al. does not render obvious the oligonucleotides and compositions thereof.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Office is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No.: C1037.70048US00.

Dated: April 28, 2010

Respectfully submitted,

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